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Europäisches Patentamt  
European Patent Office  
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(11)

EP 0 699 444 A2

(12)

## EUROPEAN PATENT APPLICATION

(43) Date of publication:

06.03.1996 Bulletin 1996/10

(51) Int Cl.<sup>6</sup>: A61K 45/06

(21) Application number: 95306124.9

(22) Date of filing: 01.09.1995

(84) Designated Contracting States:

AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL  
PT SE

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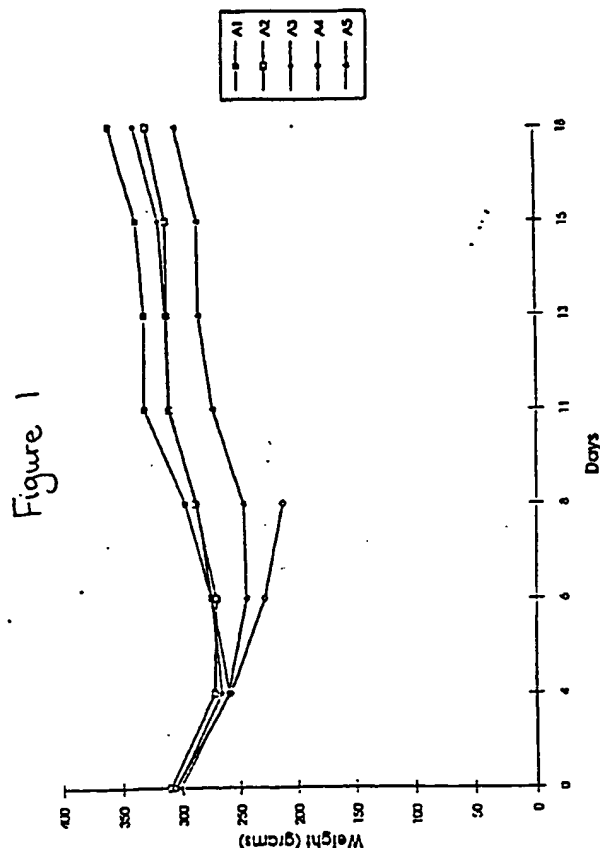
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(54) Composition for the treatment of intestinal wounds or ulcers containing proteins, carbohydrates and fat

(57) The invention relates to the manufacture of a therapeutic composition for aiding healing or preventing the onset of intestinal wounds or ulcers in a patient, reducing, or preventing, the gastrointestinal side effects associated with the administration of a nonsteroidal anti-

inflammatory drug, or treatment of arthritis. The composition includes a protein source, a carbohydrate source, a fat source, and may include a specialised vitamin and mineral profile.



## Description

**BACKGROUND OF THE INVENTION**

5 The present invention relates generally to the treatment and nutritional support of patients. More specifically, the present invention relates to the treatment of patients suffering from intestinal wounds or ulcers or at risk of same.

An ulcer is a common inflammatory lesion in which a loss or destruction of superficial tissue exists. Ulcers occur in several locations as acute, sub-acute, chronic or recurrent types. In each location, some initiating factor, such as action of bacterial toxins or lack of oxygen, causes death of the surface tissue. This necrotic tissue then usually sloughs off, leaving the underlying area exposed to further damage.

10 Peptic ulcers are a common form of ulcers that occur in the upper gastrointestinal tract. Peptic ulcer is defined as a circumscribed ulceration of the mucous membrane penetrating through the muscularis mucosa and occurring in areas exposed to acid and pepsin. The loss of the mucosa, ordinarily covered by a mucous secretion, lays bare the musculo-membranous wall. Peptic ulcers occur most commonly in the first few centimeters of the duodenum (duodenal ulcers) and along the lesser curvature of the stomach (gastric ulcers). See The Merck Manual, 16th Edition, p. 768.

15 While the peptic ulcer continues to be a common ailment in the general population, the immediate cause of such ulcer remains unknown. Emotional tension and certain physiological patterns are frequently present in affected individuals. Many influences may disturb the balance between ulcer-promoting factors (e.g., secretion of acid or pepsin into the stomach) and factors protecting the mucosal lining of the esophagus, stomach or duodenum (e.g., mucous production, membrane barriers to permeability, and replacement of shed or damaged mucosal cells). See The Merck Manual, 16th Edition, p. 768.

20 Ulcerative colitis of the large intestine is similar, in many respects, to peptic ulcer, because its exact cause is also unknown. Ulcerative colitis is defined as a chronic, non-specific, inflammatory and ulcerative disease arising in the colonic mucosa and is characterized most often by bloody diarrhea. The disease usually begins in the rectosigmoid area and may extend proximally, eventually to involve the entire colon, or it may include most of the large bowel at once. See The Merck Manual, 16th Edition, p. 834.

25 Similar to ulcerative colitis, intestinal ulceration and stricture formation are also characteristic of the inflammatory bowel disease, Crohn's disease. Crohn's disease is defined as a non-specific chronic transmural inflammatory disease that most commonly effects the distal ileum and colon. See Merck Manual, 16th Edition, p. 830. However, it may also occur in other parts of the GI tract. The disease is common and causes inflammation of the small intestine and large bowel.

30 While the immediate causes for intestinal ulcers and wounds remain uncertain, such ulcers and wounds are known to be the adverse side effect of certain drug treatments. For instance, many nonsteroidal anti-inflammatory drugs (NSAIDs) are known to cause gastrointestinal side effects. Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported in patients receiving such NSAIDs. See Physicians' Desk Reference, 48th Edition, p. 1473.

35 Prevalent areas subject to ulceration seem to be the stomach and small intestine. Patients who take NSAIDs have an increased risk of mucosal damage in the upper gastrointestinal tract. Many nonsteroidal anti-inflammatory drugs (NSAIDs) cause small intestinal inflammation that may lead to ulceration, perforation and death. See Bjarnason et al, Nonsteroidal Antiinflammatory Drug-Induced Intestinal Inflammation in Humans, Gastroenterology, Vol. 93, No. 3, pp. 480-489 (1987). Recent studies have shown that 70% of patients on long-term NSAIDs develop small intestinal inflammation. See Bjarnason et al, Clinicopathological Features of Nonsteroidal Antiinflammatory Drug-Induced Small Intestinal Strictures, Gastroenterology, Vol. 94, No. 4, pp. 1070-1074 (1988). Studies have shown a link between the use of NSAIDs and serious complications of peptic ulcer disease. Allison et al, Gastrointestinal Damage Associated with the Use of Nonsteroidal Antiinflammatory Drugs, The New England Journal of Medicine, Vol. 327, No. 11, pp. 749-753 (1992).

45 The pathogenesis of the intestinal inflammation is incompletely understood but thought to involve several interacting factors. Increased intestinal permeability is evident within hours of NSAID ingestion. Researchers have suggested that this exposes the mucosa to luminal macromolecules and toxins. In conjunction with the effect of NSAIDs on chemotaxis and neutrophil function, this may make way for bacterial invasion and hence inflammation. Id.

50 In addition to small intestinal ulceration, gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred in patients receiving NSAIDs. Researchers have also reported increased abdominal pain in ulcerative colitis patients as well as the development of ulcerative colitis and regional ileitis to occur rarely. See Physicians' Desk Reference, 48 Edition, p. 1473.

55 Still further, researchers have reported that ingested NSAIDs may cause a nonspecific colitis (in particular, fene-mates), and many patients with collagenous are taking NSAIDs. NSAIDs may also cause relapse of classic inflammatory bowel disease and contribute to serious complications of diverticular disease (fistula and perforation). Bjarnason et al, Side Effects on Nonsteroidal Anti-inflammatory Drugs on the Small and Large Intestine in Humans, Gastroenterol-

ogy, 104 (6), pp. 1832-47 (1993).

Although it is well known that NSAIDs cause or aggravate intestinal ulcers or wounds in humans, few researchers have addressed ways to prevent or reduce this adverse side effect in patients receiving such drugs. Nevertheless, NSAIDs continues to be the primary recommended drug treatment for various arthritis patients, such as patients suffering from rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. As a result thereof, patients receiving such NSAIDs as a treatment for their arthritic condition often must endure the adverse gastrointestinal side effects of such drugs.

Therefore, a need exists for a method of aiding healing or preventing the onset of intestinal wounds or ulcers in a patient at risk of same.

## 10 SUMMARY OF THE INVENTION

The present invention provides a method for treating intestinal wounds or ulcers in a patient. Additionally, the present invention provides a method for reducing or preventing gastrointestinal side effects associated with the treatment of nonsteroidal anti-inflammatory drugs.

15 In an embodiment, the present invention provides a method for aiding healing or preventing the onset of intestinal wounds or ulcers in a patient. The method includes the step of administering to the patient a therapeutically effective amount of an enteral composition.

Pursuant to the present invention, the enteral composition includes: a protein source comprising approximately 14% to about 25% of the total calories; a carbohydrate source comprising approximately 40% to about 60% of the total calories; and a fat source comprising approximately 30% to about 44% of the total calories. The fat source includes a source of medium chain triglycerides such that the composition has a medium chain triglyceride to long chain triglyceride (MCT:LCT) ratio of approximately 1:4 to 4:1. Preferably, the composition also includes a source of vitamins and minerals including approximately 75% to about 150% of the United States recommended daily allowance per 1500 Kcal of composition administered.

25 A suitable protein source pursuant to the present invention can be intact or hydrolyzed protein. In addition, the protein source may be either whey or casein.

In an embodiment, the carbohydrate source is either maltodextrin or corn starch.

In an embodiment, the composition includes fractionated coconut oil as a suitable medium chain triglyceride source.

In an embodiment, approximately 25% to about 75% of the fat source consists of medium chain triglycerides.

30 In an embodiment, the patient is at risk of intestinal wounds or ulcers due to the nonsteroidal anti-inflammatory drug the patient is receiving. In an embodiment, the nonsteroidal anti-inflammatory drug is indomethacin.

The present invention also provides a method of inhibiting the gastrointestinal side effects suffered by a patient receiving a nonsteroidal anti-inflammatory drug. The method includes the step of administering to a patient receiving the nonsteroidal anti-inflammatory drug a therapeutically effective amount of a composition comprising: a protein source; a carbohydrate source; a fat source; and a source of vitamins and minerals. The protein source comprises approximately 14% to about 25% of the total calories. The carbohydrate source comprises approximately 40% to about 60% of the total calories. And, the fat source comprises approximately 33% to about 44% of the total calories. The fat source has a MCT:LCT ratio of approximately 1:4 to 4:1. The composition further includes a source of vitamins and minerals including approximately 75% to about 150% of the recommended daily allowance per 1500 Kcal of the composition administered.

40 Still further, the present invention provides a method for treating a patient suffering from arthritis, such as rheumatoid arthritis, ankylosing spondylitis or osteoarthritis. The method comprises the step of administering to the patient a nonsteroidal anti-inflammatory drug in combination with the enteral composition of the present invention to reduce the gastrointestinal side effects of the nonsteroidal anti-inflammatory drug.

45 An advantage of the present invention is that it prevents the onset of intestinal wounds or ulcers in a patient at risk of same.

Moreover, an advantage of the present invention is that it aids in the healing of intestinal wounds or ulcers in a patients suffering from same.

50 Another advantage of the present invention is that it provides a new method for inhibiting the gastrointestinal side effects associated with the use of nonsteroidal anti-inflammatory drugs. As a result, nonsteroidal anti-inflammatory drugs, such as indomethacin, can be more effectively use in the treatment of arthritis.

Furthermore, an advantage of the present invention is that it provides a new method for treating arthritis that prevents the adverse gastrointestinal side effects commonly associated with such treatments.

Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments and from the drawings.

55

## BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1-3 illustrate the individual weights in weight (grams) versus days of tested rats treated with Peptamen®.

Nutren® and standard rat chow, respectively, pursuant to Experiment No. 2.

Figure 4 illustrates the average weight in grams (gms) versus days of the three tested rat groups pursuant to Experiment No. 2.

Figure 5 illustrates the average caloric intake in calories (cals) versus days of the three tested rat groups pursuant to Experiment No. 2.

Figure 6-8 illustrate the caloric intake in calories (cals) versus days of the rats administered Peptamen®, Nutren® and standard rat chow, respectively, pursuant to Experiment No. 2.

Figure 9 illustrates the average caloric intake in calories (cals) versus days of the three tested rat groups pursuant to Experiment No. 2.

Figure 10 illustrates the average caloric intake in calories of metabolizable energy versus days of the three tested rat groups pursuant to Experiment No. 2.

Figure 11 is a bar graph representing the mean ulcer area (mm<sup>2</sup>) of the three tested rat groups pursuant to Experiment No. 2.

Figure 12 illustrates the relationship between ulcer area and average caloric intake per day for the tested rat groups pursuant to Experiment No. 1.

#### DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

Intestinal wounds or ulcers can occur due to a number of possible causes and insults. For example, intestinal lesions and ulcers may develop in patients receiving nonsteroidal anti-inflammatory drugs.

Such nonsteroidal anti-inflammatory drugs are of proven value in various forms of arthritis. Among others, the following NSAIDs have been recommended for patients suffering from arthritis: salicylates; indomethacin; ibuprofen; naproxen; fenoprofen; tolmetin; sulindac; meclofenamate; ketoprofen; piroxicam; and diclofenac. Unfortunately, however, tolerance or potential toxic risks rather than marginal differences in efficacy dictate the drug choice. Patients receiving such NSAIDs have an increased risk of mucosal damage in the upper gastrointestinal tract.

Indomethacin is a common nonsteroidal drug with anti-inflammatory, antipyretic and analgesic properties. An untoward effect of indomethacin therapy is gastrointestinal bleeding and ulceration. Such bleeding and ulceration increases with larger doses of indomethacin. As a result, this dose dependency thereby limits the therapeutic approaches that can be taken with such a compound.

The inventor believes that the use of an enteral diet when administered to a patient at risk of intestinal wounds or ulcers will reduce or prevent such conditions. Specifically, the inventor believes that the use of a composition containing protein, carbohydrate and fat sources as well as a source of vitamins and minerals will be effective in the treatment of intestinal ulceration.

The protein source includes approximately 14% to about 25% of the total calories of the composition. In a preferred embodiment, proteins provide approximately 16% of the caloric content of the composition. The protein source may include either hydrolyzed or intact protein. In addition, the protein source may be either whey or casein. In an embodiment, hydrolyzed proteins, such as hydrolyzed lactalbumin extracted from whey, can be utilized pursuant to the present invention.

Carbohydrates provide approximately 40% to about 60% of the caloric content of the composition. In a preferred embodiment, carbohydrates provide approximately 51% of the caloric content. A number of carbohydrates can be used including maltodextrin or hydrolyzed corn starch.

The fat content is approximately 33% to about 44% of the caloric content of the composition. In a preferred embodiment, the fat content comprises approximately 33% of the total caloric content of the composition.

Preferably, the fat source has a MCT:LCT ratio of 1:4 to 4:1. In an embodiment, approximately 25 to 75% of the fat source consists of medium-chain triglycerides. In a preferred embodiment, the medium chain triglyceride source is fractionated coconut oil.

In an embodiment, the fat source of the composition includes a source of omega-3 and a source of omega-6 fatty acids. Preferably, the omega-6 to omega-3 fatty acid ratio is approximately 4:1.

In addition, the present invention preferably includes a specialized vitamin and mineral profile. The composition includes a source of vitamins and minerals including approximately 75% to about 150% of the recommended daily allowance per 1500 Kcal of the composition administered. In an embodiment, ultra-trace minerals, such as carnitine and taurine, are included in the composition.

The composition of the present invention is a ready-to-use enteral formulation. The composition can be tube-fed to a patient, or fed by having the patient drink same. Preferably, the caloric density of the composition is 1.0 Kcal per ML.

The composition of the present invention can be used for aiding healing of intestinal wounds or ulcers in a patient suffering from same. Likewise, the composition can be used for preventing the onset of intestinal wounds or ulcers in a patient at risk of same. For these treatments, the composition can be administered alone.

Additionally, the composition of the present invention can be used to inhibit the gastrointestinal side effects suffered

by a patient receiving a nonsteroidal anti-inflammatory drug. To this end, the composition of the present invention can be administered either contemporaneously or on the same days as the nonsteroidal anti-inflammatory drug.

Moreover, the composition of the present invention can be utilized in an improved method for treating patients suffering from arthritis. The method includes the step of administering the composition of the present invention in conjunction with the nonsteroidal anti-inflammatory drug, e.g., indomethacin. Again, the composition can be administered either contemporaneously or on the same days as the nonsteroidal anti-inflammatory drug.

By way of example, and not limitation, examples of suitable compositions that may be used pursuant to the present invention are as follows:

#### Composition No. 1

A suitable composition that may be utilized pursuant to the present invention is sold under the trademark Peptamen® and can be obtained from Clintec Nutrition Company. Peptamen® is a complete, liquid, ready-to-use, isotonic, peptide-based elemental diet. The Peptamen® elemental diet has a low osmolality (270 mOsm/kg water) allowing feeding to be initiated at full strength.

Peptamen® includes the following ingredients: water; maltodextrin; hydrolyzed whey protein; medium-chain triglycerides (MCT source: fractionated coconut oil); corn starch; sunflower oil; soy lecithin; potassium citrate; sodium phosphate; magnesium chloride; guar gum; calcium phosphate; choline chloride; sodium ascorbate (vit. C); calcium citrate; magnesium oxide; taurine; L-carnitine; citric acid; zinc sulfate; ferrous sulfate; niacinamide (A B-vit); DL-alpha tocopheryl acetate (vit. E); retinyl palmitate (vit. A); calcium pantothenate (A B- vit); manganese sulfate; pyridoxine hydrochloride (vit. B<sub>6</sub>); cholecalciferol (vit. D<sub>3</sub>); copper sulfate; riboflavin (vit. B<sub>2</sub>); thiamine mononitrate (vit. B<sub>1</sub>); folic acid; biotin; potassium iodide; sodium molybdate; phyloquinone (vit. K<sub>1</sub>); sodium selenate; chromium chloride; and cyanocobalamin (vit. B<sub>12</sub>).

Peptamen® has the following nutrient composition (based on 8.45 Fl oz (250 ml)):

N u t r i e n t			
	<u>Composition</u>	<u>Amount</u>	<u>%U.S. RDA*</u>
5	Protein	10 g	**
	Carbohydrate	31.8 g	22
	Fat***	9.8 g	**
	Water	220 ml	**
	Vitamin A	1000 I.U.	20
10	Vitamin D	70 I.U.	18
	Vitamin E	7 I.U.	23
	Vitamin K	20 mcg	**
	Vitamin C	35 mg	58
	Thiamine (B <sub>1</sub> )	.5 mg	33
15	Riboflavin (B <sub>2</sub> )	.6 mg	35
	Niacin	7 mg	35
	Vitamin B <sub>6</sub>	1 mg	50
	Folic Acid	135 mcg	34
	Pantoic Acid	3.5 mg	35
20	Vitamin B <sub>12</sub>	2 mcg	33
	Biotin	100 mcg	33
	Choline	112 mg	**
	Taurine	20 mg	**
	L-Carnitine	20 mg	**
25	Calcium	200 mg	20
	Phosphorus	175 mg	18
	Magnesium	100 mg	25
	Zinc	3.5 mg	23
	Iron	3 mg	17
30	Copper	.35 mg	18
	Manganese	.68 mg	**
	Iodine	25 mcg	17
	Sodium	125 mg	**
	Potassium	313 mg	**
35	Chloride	250 mg	**
	Chromium	10 mcg	**
	Molybdenum	30 mcg	**
	Selenium	10 mcg	**
40	*%U.S. RDA Recommended daily allowance for adults & children 4 or more years of age		
	** U.S. RDA not established		
	***MCT Provides 6.75 grams/250 ml		

#### Composition No. 2

Another suitable composition that may be utilized in the present invention is sold under the trademark Nutren® 1.0. Nutren® 1.0 can also be obtained from Clintec Nutrition Company. Nutren® 1.0 is a balanced nutritional formula that is lactose and gluten-free.

Nutren® 1.0 includes the following ingredients: water; maltodextrin; calcium-potassium caseinate; canola oil; medium-chain triglycerides (MCT source: fractionated coconut oil); corn oil; sodium citrate; soy lecithin; potassium phosphate; citric acid; calcium citrate; potassium chloride; magnesium chloride; choline chloride; sodium ascorbate; sodium phosphate; carrageenan; magnesium oxide; L-carnitine; taurine; zinc sulfate; ferrous sulfate; DL-alpha tocopheryl acetate; niacinamide; retinyl palmitate; calcium pantothenate; manganese sulfate; pyridoxine hydrochloride; copper sulfate; riboflavin; thiamine; folic acid; biotin; cholecalciferol; potassium iodide; sodium molybdate; sodium selenate; phylloquinone; chromium chloride; and cyanocobalamin.

Nutren® 1.0 has the following nutrient composition (based on 8.45 Fl oz (250 ml)):

	<u>N u t r i e n t</u> <u>Composition</u>	<u>Amount</u>	<u>%U.S. RDA*</u>
5	Protein	10 g	**
	Carbohydrate	31.8 g	22
	Fat***	9.5 g	**
	Water	213 ml	**
10	Vitamin A	1000 I.U.	20
	Vitamin D	70 I.U.	17
	Vitamin E	7 I.U.	23
	•Vitamin K	12.5 mcg	**
	Vitamin C	35 mg	58
15	Thiamine (B <sub>1</sub> )	.5 mg	33
	Riboflavin (B <sub>2</sub> )	.6 mg	35
	Niacin	7 mg	35
	Vitamin B <sub>6</sub>	1 mg	50
20	Folic Acid	135 mcg	33
	Pantoic Acid	3.5 mg	35
	Vitamin B <sub>12</sub>	2 mcg	33
	Biotin	100 mcg	33
	Choline	113 mg	**
25	Taurine	20 mg	**
	L-Carnitine	20 mg	**
	•Calcium	167 mg	17
	•Phosphorus	167 mg	17
	•Magnesium	67 mg	17
30	Zinc	3.5 mg	23
	Iron	3 mg	17
	Copper	.35 mg	17
	Manganese	.68 mg	**
	Iodine	25 mcg	17
35	•Sodium	219 mg	**
	•Potassium	312 mg	**
	•Chloride	300 mg	**
	Chromium	10 mcg	**
	Molybdenum	30 mcg	**
40	Selenium	10 mcg	**

•Indicates modified levels

\*%U.S. recommended daily allowance for adults & children  
4 or more years of age

\*\* U.S. RDA not established

\*\*\*MCT provides 2.4 grams/250 ml

By way of example, and not limitation, experimental results illustrating the use of the present invention to treat intestinal ulcers will now be set forth.

#### EXPERIMENT NO. 1

This experiment was conducted to evaluate whether two compositions would aid in the healing of indomethacin-induced ulceration in animals. The two compositions were Metronizadole, an antibiotic, and Petamen®.

A single injection of indomethacin (12.5 g/mg s.c.) was given to male Wistar rats, weighing approximately 300 grams. The control animals (N=10) received no treatment. Ten animals received metronidazole dosages of 32 +/- 4 mg/kg/day. Lastly, twelve animals received Peptamen® dosages of 57 +/- 1 ml/day. All except the animals treated with Peptamen® received rat chow ad libitum.



After fifteen (15) days, the animals were sacrificed, the intestine excised and the ulcer area measured by planimetry. A second control group was sacrificed after 60 days and tested similar to the other animals. Ulcer area was measured in mm<sup>2</sup>. Table 1 below sets forth the test results.

TABLE 1

Control (15 d.)	Metron.	Peptamen®	Control (60 d.)
166 +/- 42	191 +/- 59	17 +/- 7	477 +/- 185

As Table 1 illustrates, metronidazole did not effect the ulcer healing; whereas Peptamen® significantly ( $p < 0.001$ ) reduced ulcer area. No spontaneous healing occurred since the ulcer area of the second control group at 60 days was similar to the control group at 15 days. While one animal that was unable to take adequate Peptamen® (31 ml/day,  $p < 0.005$ ) had extensive ulceration, three Peptamen® treated animals had a normal intestine, which was not detected with any other group. Accordingly, the composition of the present invention (Peptamen®) aids in the healing of intestinal ulcers.

## EXPERIMENT NO. 2

This experiment was conducted to determine the effect of three compositions (Peptamen®, Nutren® and rat chow) on rats suffering intestinal ulceration. Each diet group consisted of five rats that were tested over a fifteen day exposure time.

All of the tested rats were initially administered a 12.5 mg/kg dosage of indomethacin to induce small intestinal ulcers. Then, over the fifteen days, each of the three group was feed the respective diet to compare the course of the ulcerations. The following parameters were recorded for each rat group over the fifteen day testing period: weight change (grams); daily caloric intake (cal); and ulcer area (mm<sup>2</sup>).

Table 2 below sets forth the weights of the individual rats in each group, namely Peptamen®, Nutren® and rat chow, respectively, as well as the average of each group. Table 3 sets forth a comparison of the weights of the respective rats between groups and at the beginning and the end of the trial testing period. As these results demonstrate, no significant difference exists between the groups with regard to weight. However, rats in all groups weighed less at the end of the trial period than they did at the beginning.

TABLE 2

Day	0	4	6	8	11	13	15	18
Peptamen (group avg)	306	263	258	265.4	305.25	309.25	313	332.25
Nutren (group avg)	309.2	266	250	242.8	268.8	277.4	285.2	309.2
rat chow (group avg)	306	264.2	253.6	258.8	298.5	304	310.5	322.75
Peptamen (individual weights)								
A1	306	259	274	296	330	330	337	359
A2	310	272	270	287	309	311	312	328
A3	305	266	274	286	310	312	318	338
A4	307	258	228	212				
A5	302	260	244	246	272	284	285	304
Nutren (individual weights)								
B1	300	249	250	241	275	283	297	320
B2	314	257	237	230	247	265	264	286
B3	305	267	239	225	233	244	248	278
B4	317	275	250	240	281	288	300	322
B5	310	282	274	278	308	307	317	340

rat chow (individual weights)								
C1	308	268	240	224				
C2	297	255	250	248	271	286	302	317
C3	302	254	247	255	291	292	300	315
C4	315	290	277	292	325	326	333	345
C5	308	254	254	275	307	302	307	314

TABLE 3

	Avg starting wt.(g)	Std dev	Avg wt. at the end	Std dev
Peptamen	321.40	13.70	303.05	25.78
Nutren	324.42	14.74	295.53	23.74
rat chow	323.91	14.71	300.91	31.32
P values (for avg starting wts.)    P values (for avg ending wts)				
Peptamen-Nutren	0.51	0.33		
Peptamen-Chow	0.56	0.80		
P values (for difference between starting and ending wts.)				
Peptamen		8.77E-03		
Nutren		9.26E-05		
rat chow		4.01E-03		

Figures 1-3 graphically set forth the individual weights in weight (grams) versus days of the rats on the Peptamen®, Nutren® and standard rat chow, respectively. Figure 4 is a graph of the average weight in weight (grams) versus days of the three groups. With respect to Figure 4, the rats were injected with indomethacin on day 1 and the controlled diets began on day 4.

Tables 4A and 4B set forth the daily caloric intake (Kcal) for the rats administered the Peptamen®, Nutren® and rat chow diets. Day 1 represents 72 hours after the rats were injected with 12.5 mg/kg of indomethacin. On day 1, all rats were given 100 calories of the respective diets. On days 2 and 3, Bx and Cx were offered only as much as Ax ate on the previous day. On day 4, paired feeding was ok, A1 was offered 120 calories as it consistently ate all it was given; C4 and C5 were given as much as designed only on days 4-7 (to compensate for paired underfeeding on days 2 and 3). Otherwise, the rats were all offered 100 calories of the respective diets each day. Table 5 sets forth the average total caloric intake (over 15 days) of the three groups of rats.

TABLE 4A

Day	1	2	3	4	5	6	7	8
Peptamen (group avg)	55.8	53.8	61.2	78.8	91.75	94.75	92.75	97.25
Nutren (group avg)	48	35.2	28.2	61	76.4	82.6	84.4	91
rat chow (group avg)	59.2	45	36	103.6	113.8	117	116.5	101.75
Peptamen (individual weights)								
A1	73	96	96	121	112	115	110	115
A2	62	68	72	89	89	82	88	91
A3	75	76	81	98	87	90	92	91
A4	12	7	15	12	Sacrificed (gastric and duodenal dilation, mid-jejunal ulcer)			
A5	57	32	42	74	79	82	81	92
Nutren (individual intake)								
B1	57	60	52	50	83	94	93	93
B2	27	22	20	42	80	80	84	92
B3	23	26	30	29	50	57	56	73
B4	30	12	8	66	77	88	95	100
B5	95	56	31	98	92	94	94	97
rat chow (individual intake)								
C1	10	22	18	26	0	Sacrificed (gastric and duodenal dilation, distal duodenal mass)		
C2	88	66	62	88	102	102	102	101
C3	44	62	57	84	102	102	102	102
C4	101	13	8	162	175	132	132	102
C5	75	62	35	158	190	132	130	102

TABLE 4B

Day	9	10	11	12	13	14	15
Peptamen (group avg)	90.75	96.5	92.75	90.5	96	96.25	96.5
Nutren (group avg)	90.8	91.4	89.8	93	92.6	96	94.2
rat chow (group avg)	102	102	102	102	102	102	102
Peptamen (individual weights)							
A1	109	116	111	107	115	111	108
A2	78	91	91	88	92	93	91
A3	89	92	87	85	89	95	92
A4	Sacrificed (gastric and duodenal dilation, mid-jejunal ulcer)						
A5	87	87	82	82	88	86	95
Nutren (individual intake)							
B1	93	92	92	93	90	96	95
B2	97	89	87	95	97	100	92
B3	73	78	81	87	87	91	94
B4	96	100	91	92	91	94	94
B5	95	98	98	98	98	99	96
rat chow (individual intake)							
C1	Sacrificed (gastric and duodenal dilation, distal duodenal mass)						
C2	102	102	102	102	102	102	102
C3	102	102	102	102	102	102	102
C4	102	102	102	102	102	102	102
C5	102	102	102	102	102	102	102

TABLE 5

	Total Cals	Std dev
Peptamen	982.95	224.68
Nutren	953.26	172.95
rat chow	966.74	173.85
	P values	
Peptamen-Nutren	0.64	
Peptamen-Chow	0.79	
Nutren-Chow	0.80	

Figure 5 is a graph of the average caloric intake in calories versus days of the three groups. With respect to this figure, one should note that rats were first weighed on the day of injection (day -2). Day 1 is the first day of the controlled diets. Figures 6-8 graphically detail the caloric intake in calories versus days of the rats administered Peptamen®, Nütren® and standard rat chow, respectively. Figure 9 is a graph detailing the average caloric intake in calories versus days of the three groups. Figure 10 is a graph detailing the average caloric intake in calories of metabolizable energy versus days of the three groups.

Lastly, the ulcer area (mm<sup>2</sup>) was measured for each rat by planimetry. Figure 11 is a bar graph representing the mean ulcer area (mm<sup>2</sup>) of the three groups. Figure 12 graphically represents the relationship between ulcer area and average caloric intake per day of the rats.

It will be understood that various modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

#### Claims

1. Use in the manufacture of a therapeutic composition for aiding healing, or preventing the onset, of intestinal wounds or ulcers in a patient of:-
  - a protein source comprising approximately 14% to about 25% of the total calories;
  - a carbohydrate source comprising approximately 40% to about 60% of the total calories; and
  - a fat source comprising approximately 33% to about 44% of the total calories, the fat source including a medium-chain triglyceride to long chain triglyceride ratio of approximately 1:4 to 4:1.
2. Use according to Claim 1 for the purpose of treating a patient at risk of intestinal wounds or ulcers because the patient is receiving a nonsteroidal anti-inflammatory drug.
3. Use in the manufacture of a therapeutic composition for inhibiting the gastrointestinal side effects suffered by a patient receiving a nonsteroidal anti-inflammatory drug, of:-
  - a protein source comprising approximately 14% to about 25% of the total calories;
  - a carbohydrate source comprising approximately 40 % to about 60 % of the total calories;
  - a fat source comprising approximately 33 % to about 44% of the total calories, the fat source including a medium-chain triglyceride to long chain triglyceride ratio of approximately 1:4 to 4:1; and
  - a source of vitamins and minerals including approximately 75 % to about 150% of the recommended daily allowance per 1500 Kcal of the composition administered.
4. Use according to Claim 3 for treating a patient to whom the composition is administered contemporaneously with the nonsteroidal anti-inflammatory drug.
5. Use in the manufacture of a composition for treating arthritis in a patient to whom a nonsteroidal anti-inflammatory drug has been or is to be administered, the composition comprising:
  - a protein source comprising approximately 14% to about 25% of the total calories;
  - a carbohydrate source comprising approximately 40 % to about 60% of the total calories; and
  - a fat source comprising approximately 33% to about 44% of the total calories, the fat source including a medium-chain triglyceride to long chain triglyceride ratio of approximately 1:4 to 4:1.
6. Use in the manufacture of a therapeutic preparation for treating arthritis of:-
  - a nonsteroidal anti-inflammatory drug and a composition comprising:
  - a protein source comprising approximately 14% to about 25% of the total calories;
  - a carbohydrate source comprising approximately 40 % to about 60% of the total calories; and
  - a fat source comprising approximately 33% to about 44% of the total calories, the fat source including a medium-chain triglyceride to long chain triglyceride ratio of approximately 1:4 to 4:1.
7. Use according to Claim 3, 4, 5 or 6 wherein the nonsteroidal anti-inflammatory drug is indomethacin.
8. Use according to any preceding claim wherein the protein source includes hydrolysed whey.
9. Use according to any one of Claims 1 to 7 wherein the protein source includes casein.

10. Use according to any preceding claim wherein the carbohydrate source is selected from maltodextrin and corn starch.
- 5 11. Use according to any preceding claim wherein the fat source includes approximately 25% to 75% medium chain triglycerides.
12. Use according to any preceding claim wherein the composition includes fractionated coconut oil as a source of medium chain triglycerides.
- 10 13. Use according to any preceding claim wherein the composition is administrable enterally.

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Figure 1

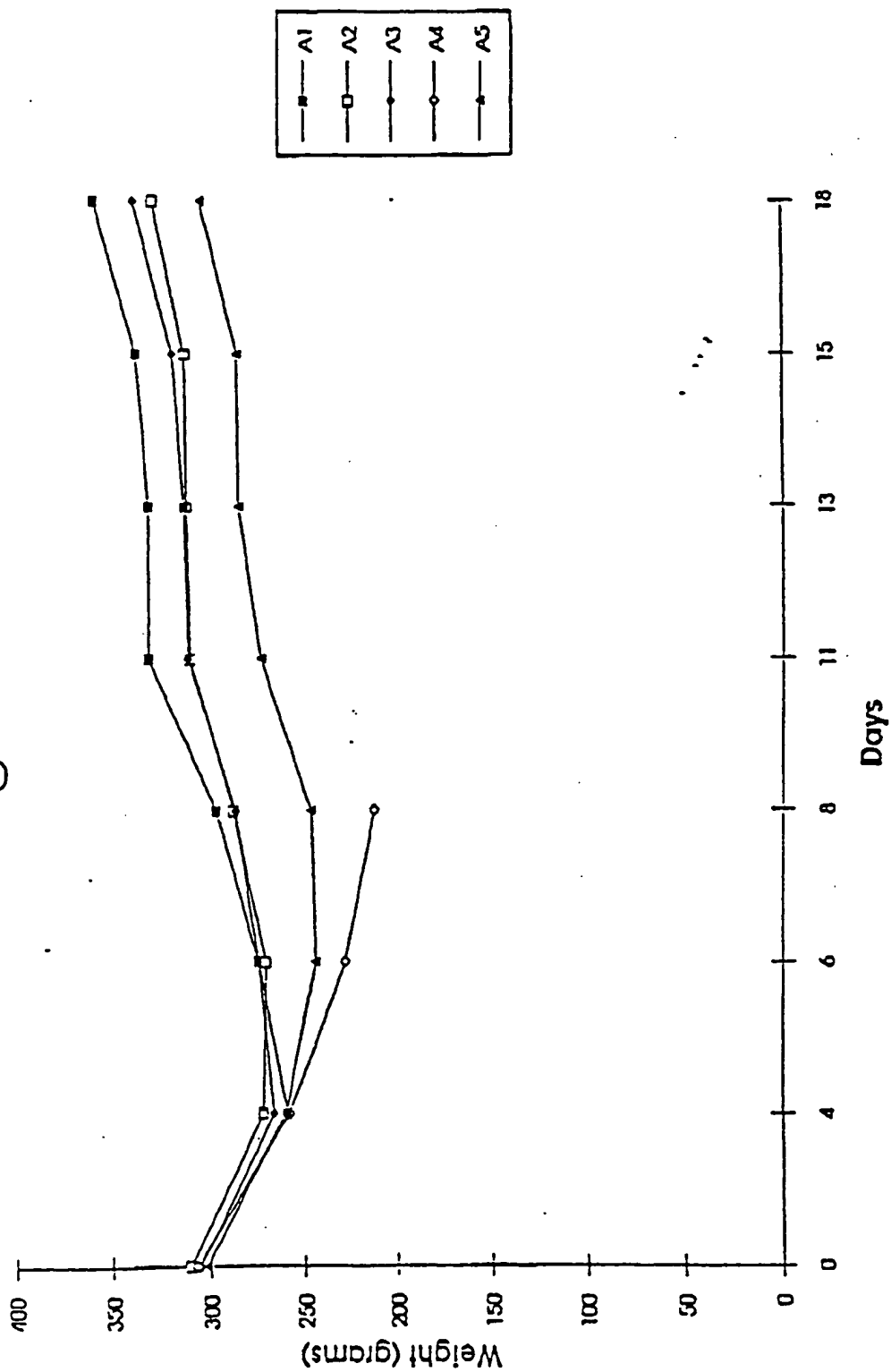


Figure 2

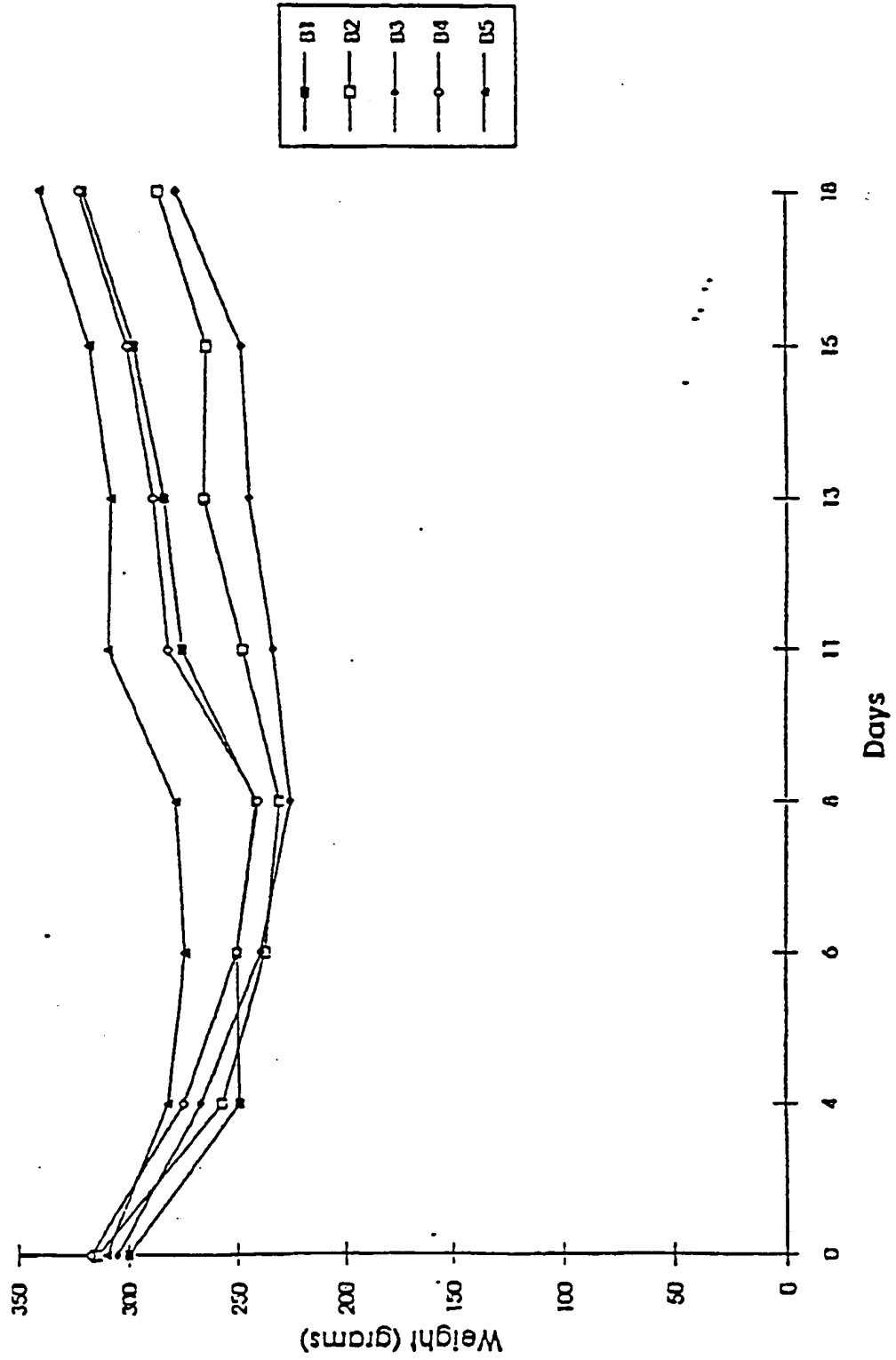




Figure 3

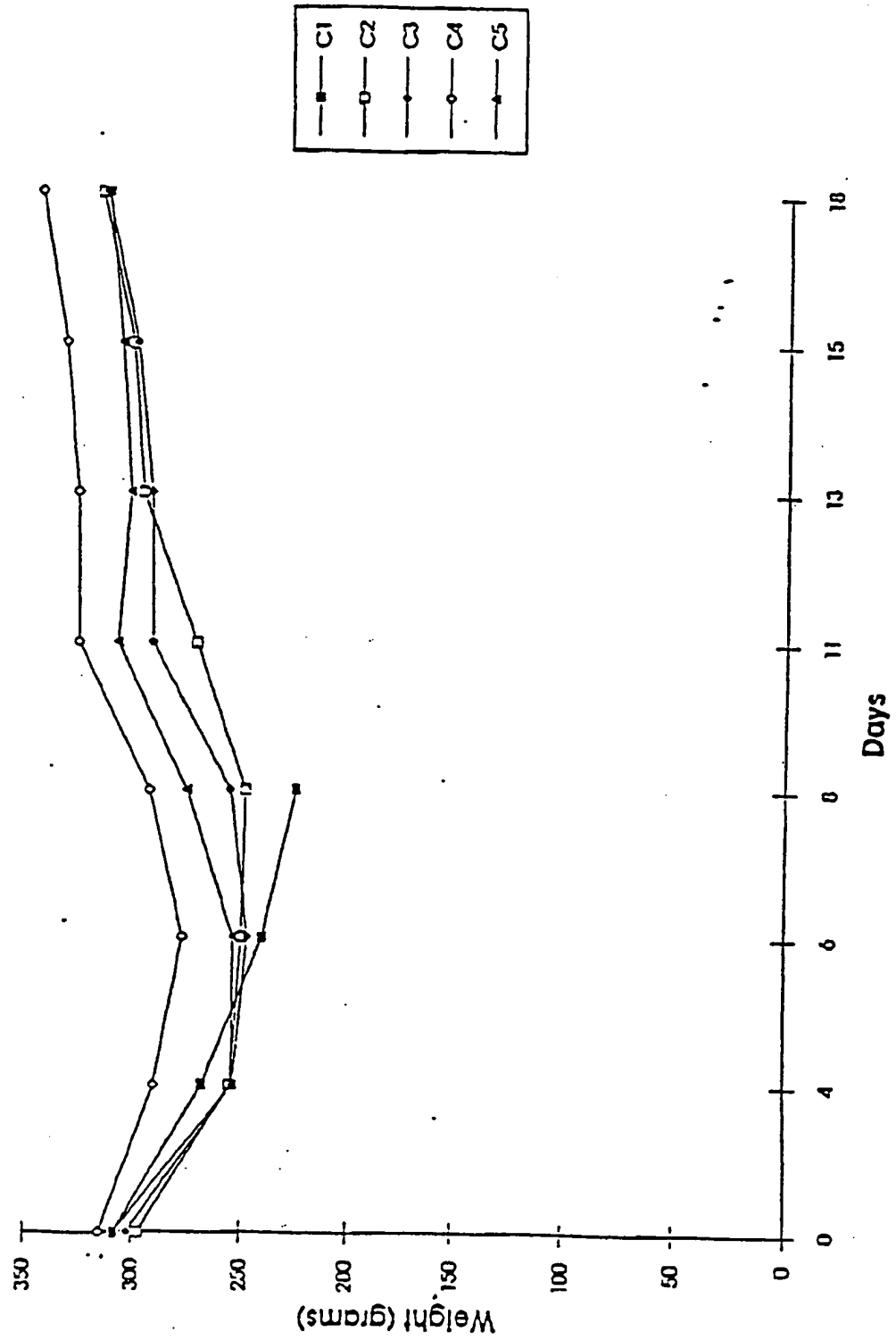
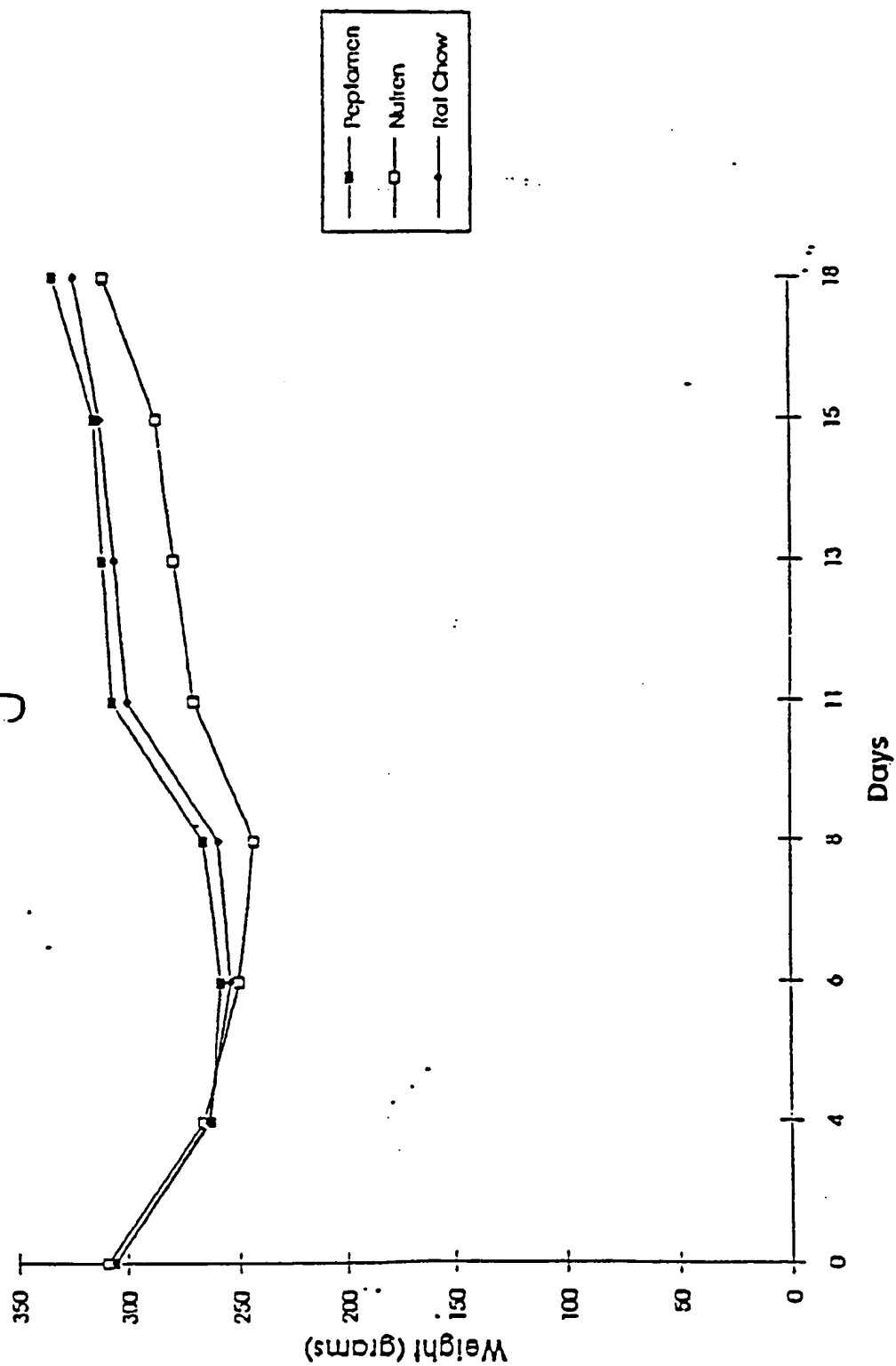


Figure 4



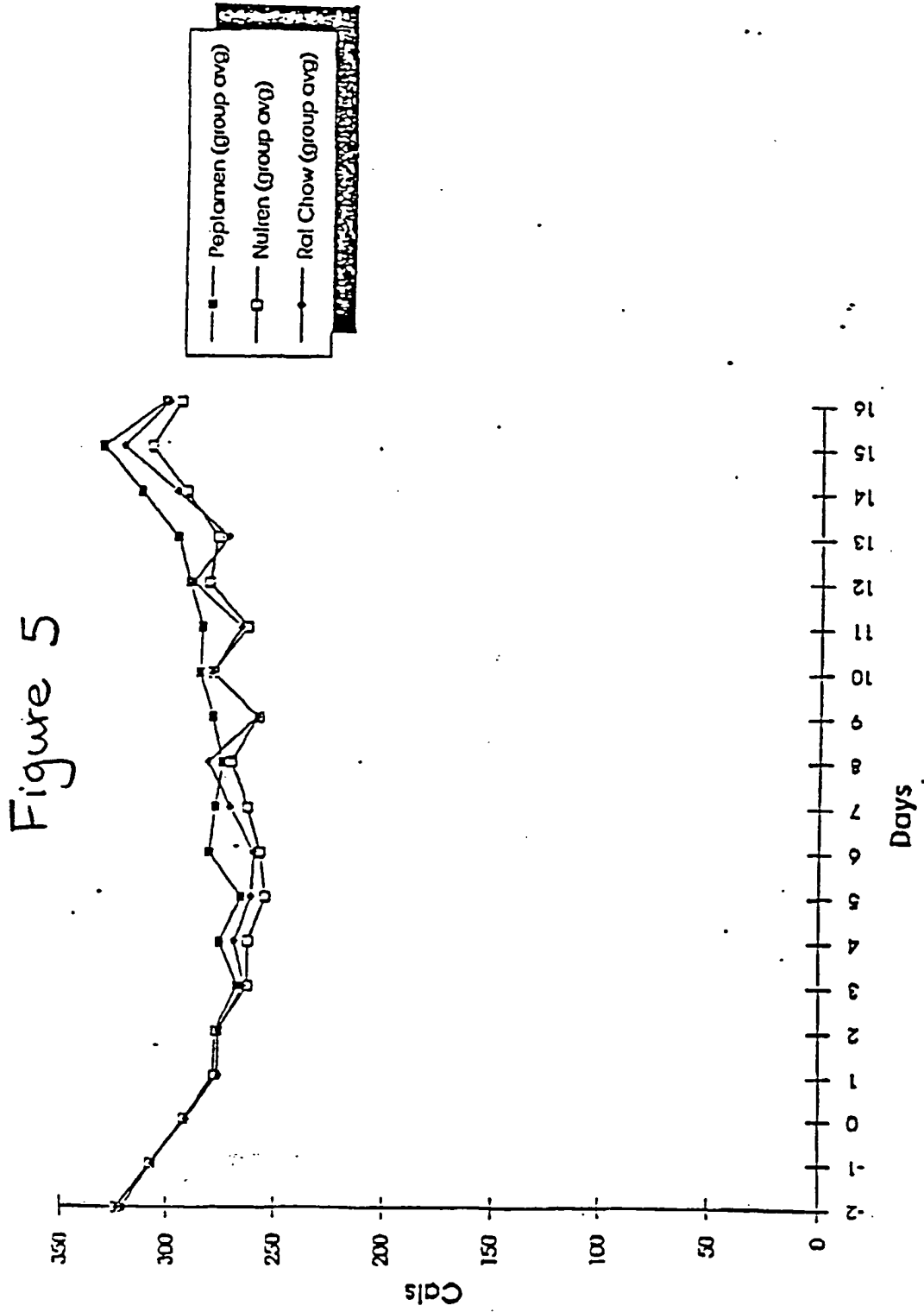


Figure 6

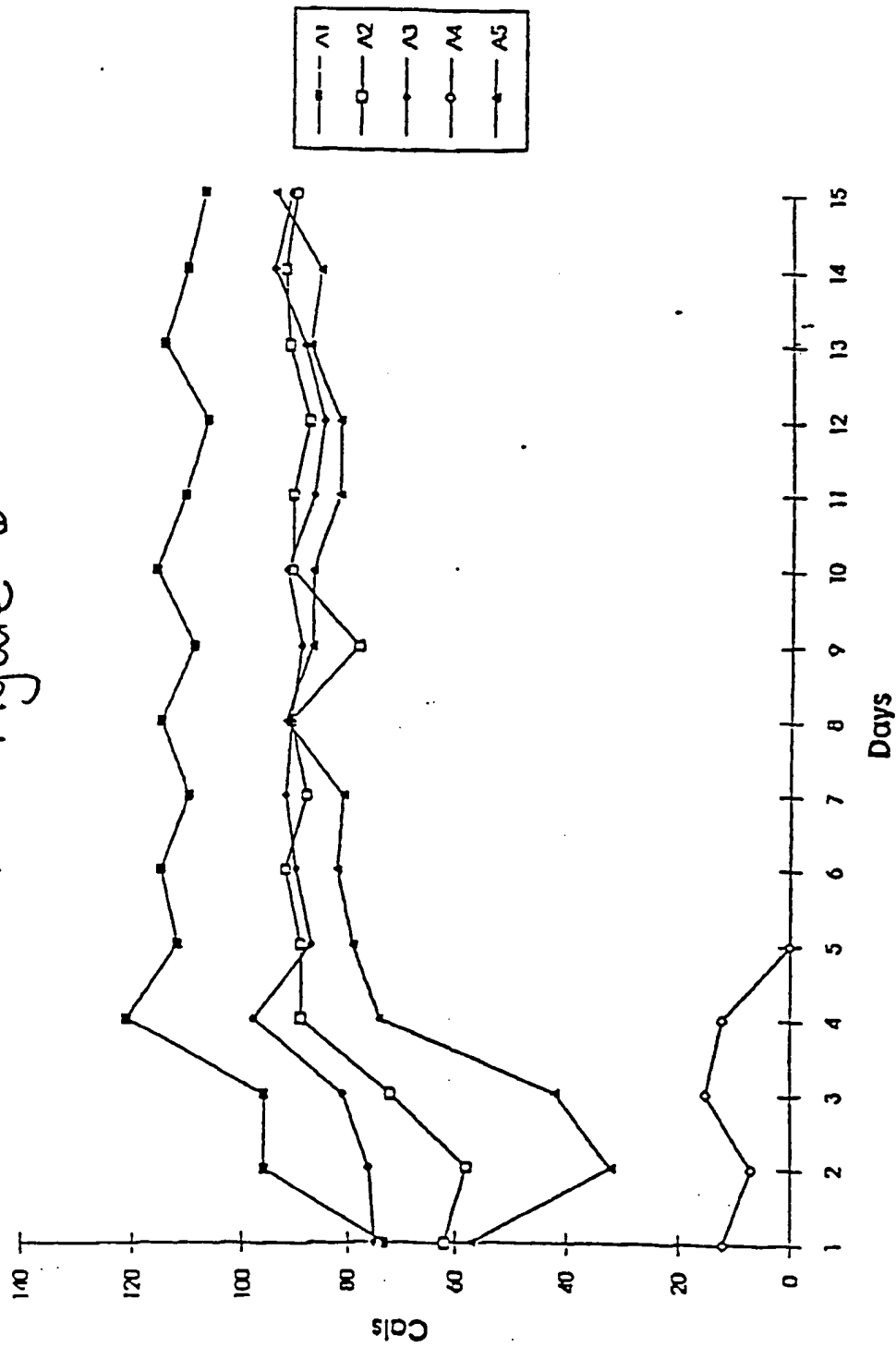


Figure 7

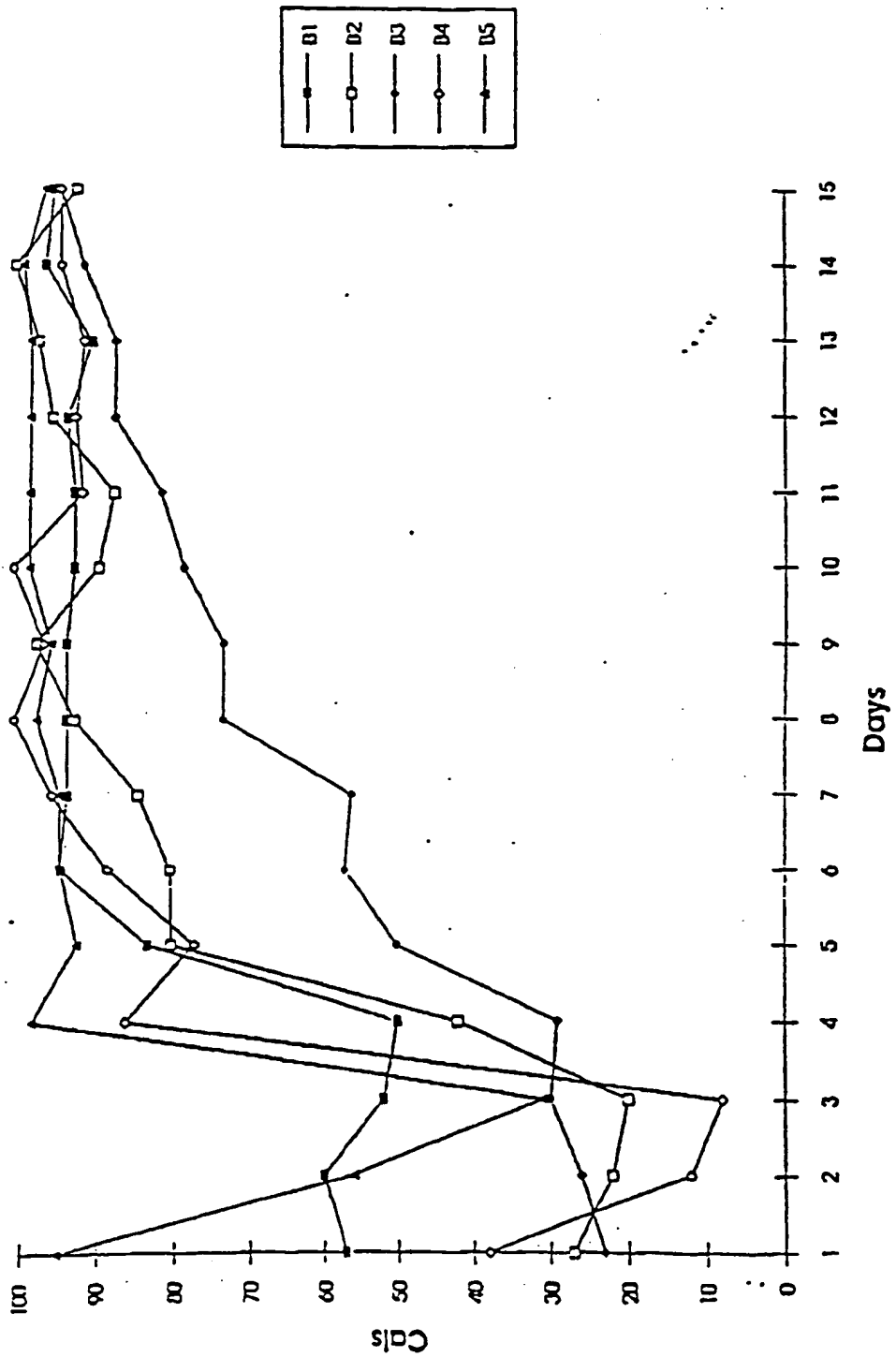


Figure 8

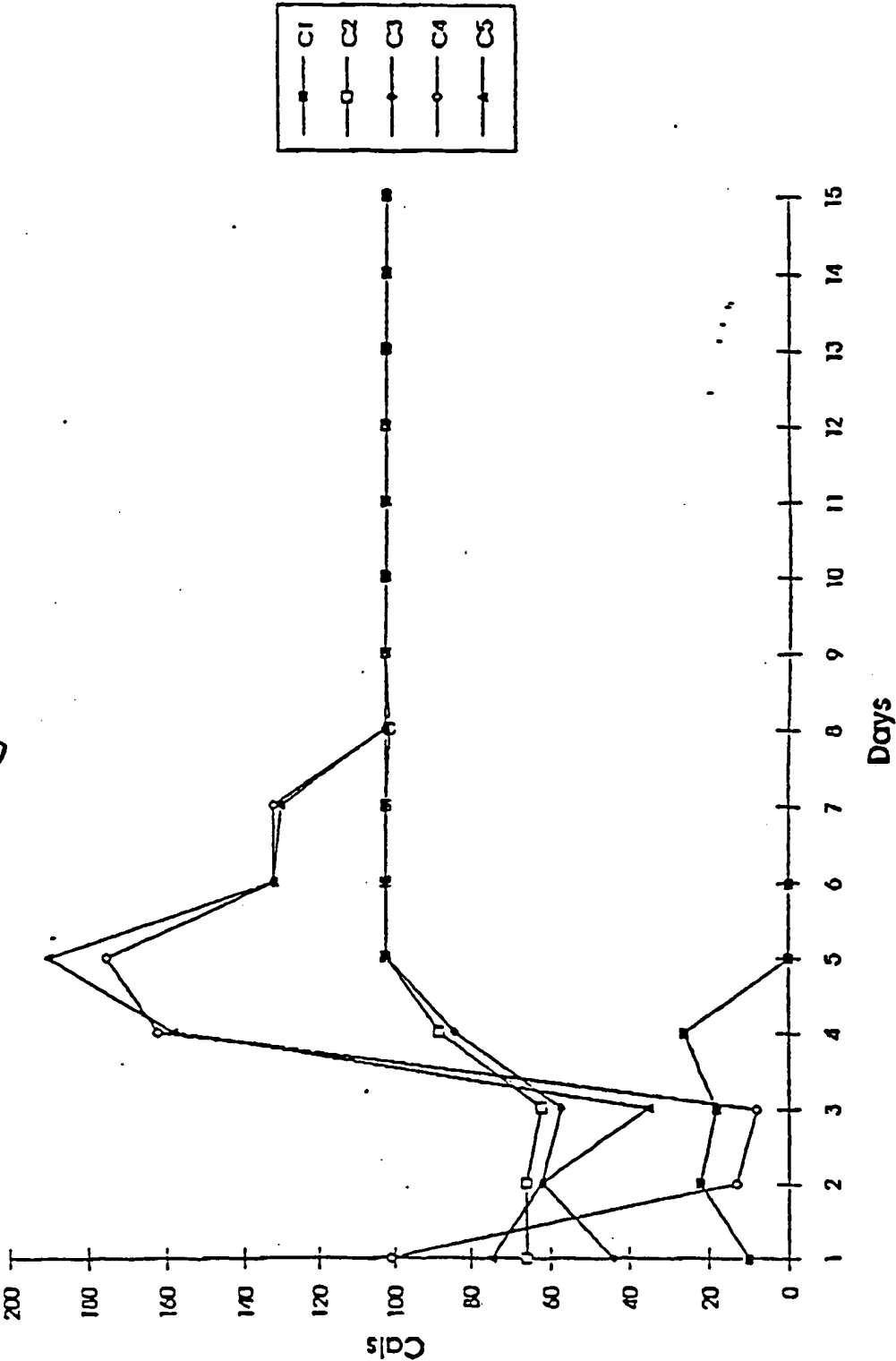


Figure 9

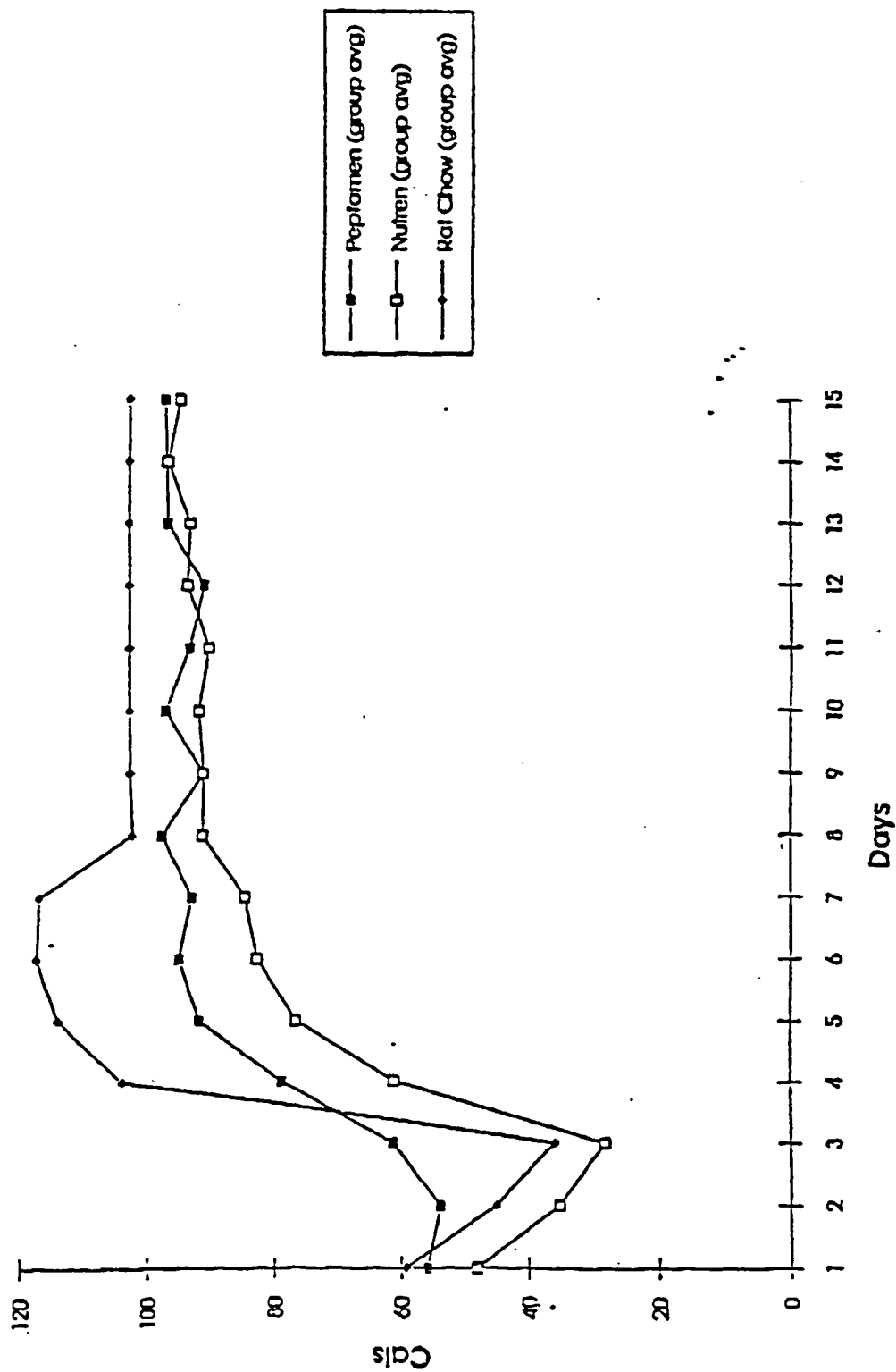


Figure 10

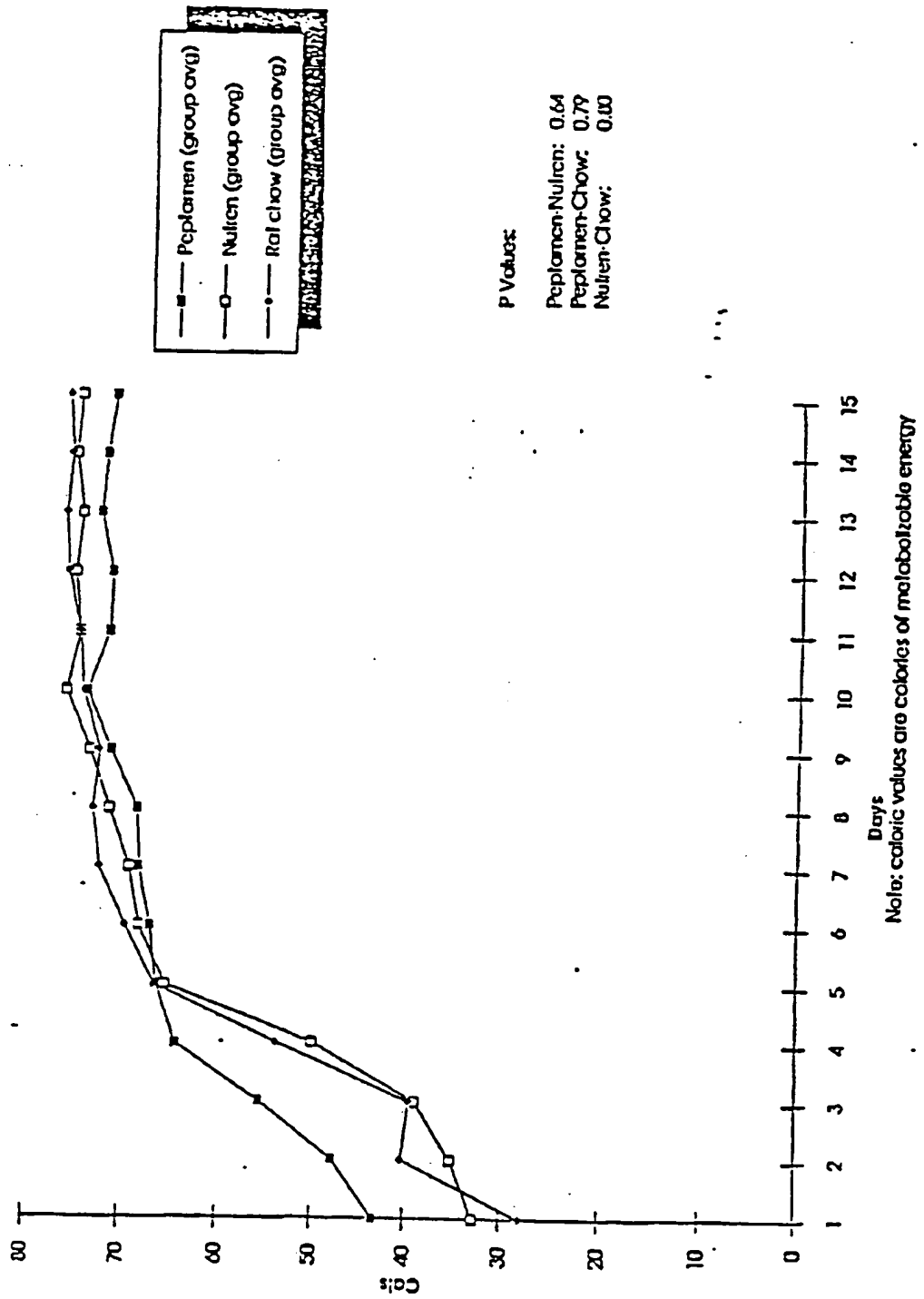




Figure 11

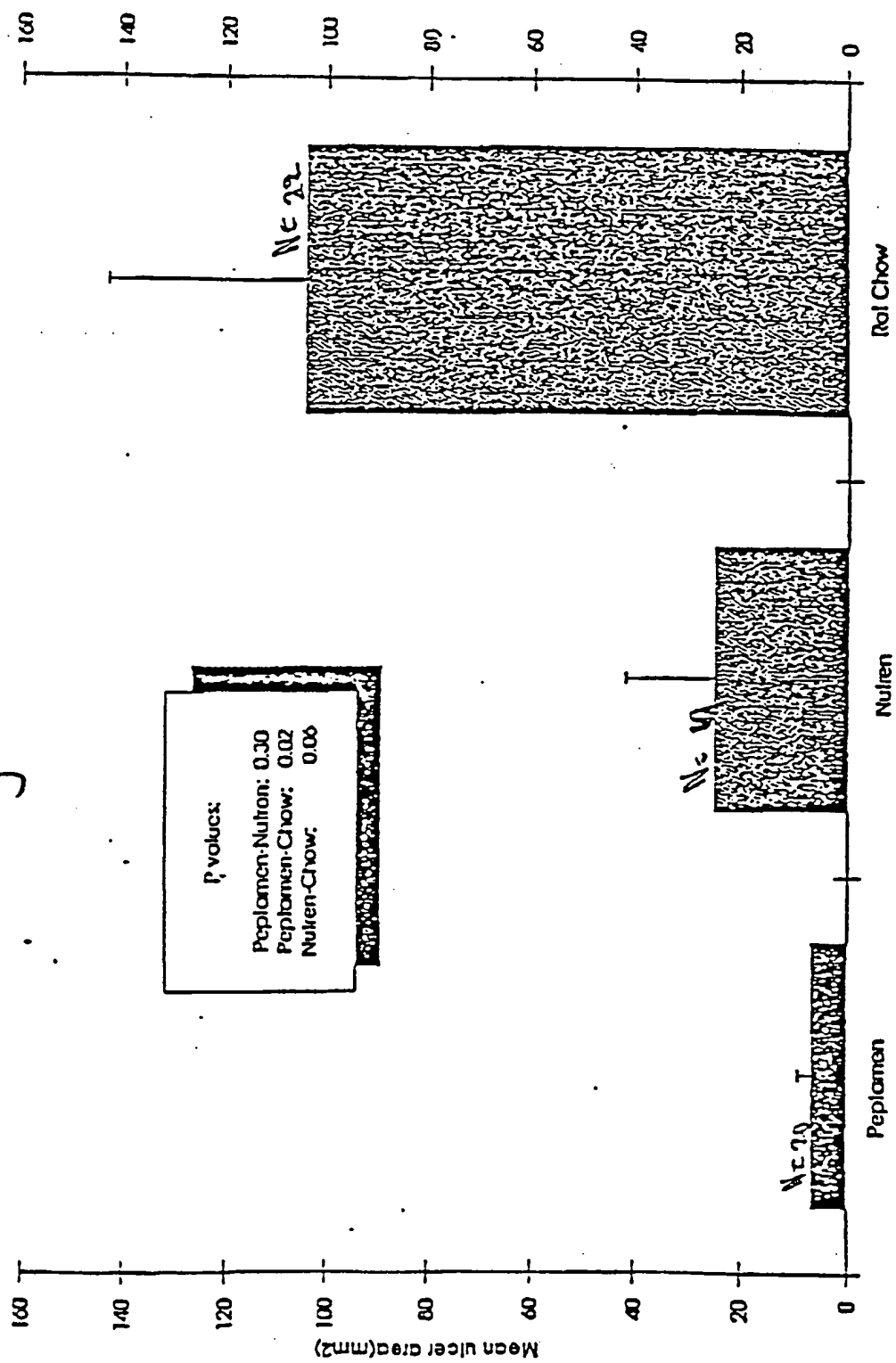
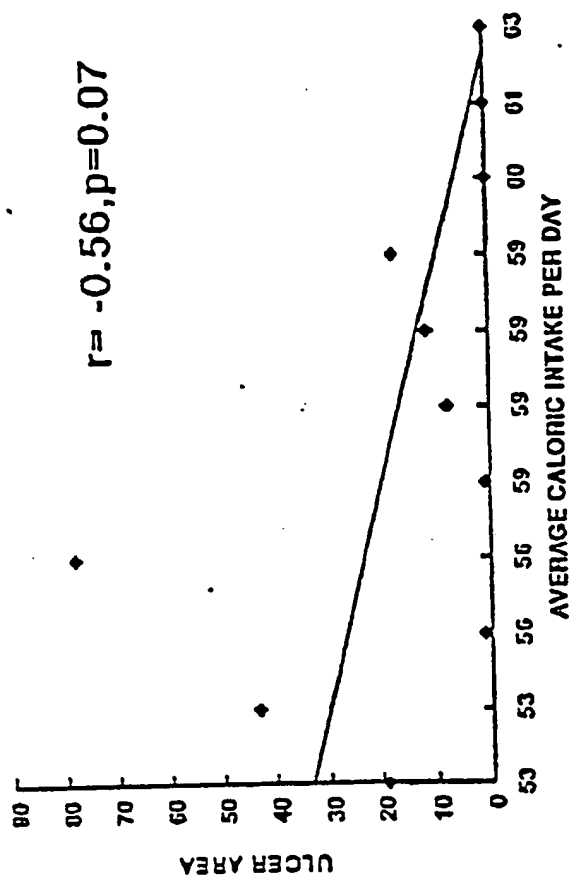
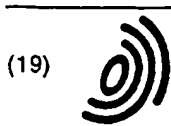


Figure 12

RELATIONSHIP CALORIES/AREA





Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) EP 0 699 444 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:  
12.05.1999 Bulletin 1999/19

(51) Int Cl.<sup>6</sup>: A61K 45/06

(43) Date of publication A2:  
06.03.1996 Bulletin 1996/10

(21) Application number: 95306124.9

(22) Date of filing: 01.09.1995

(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL  
PT SE

(30) Priority: 02.09.1994 US 300428

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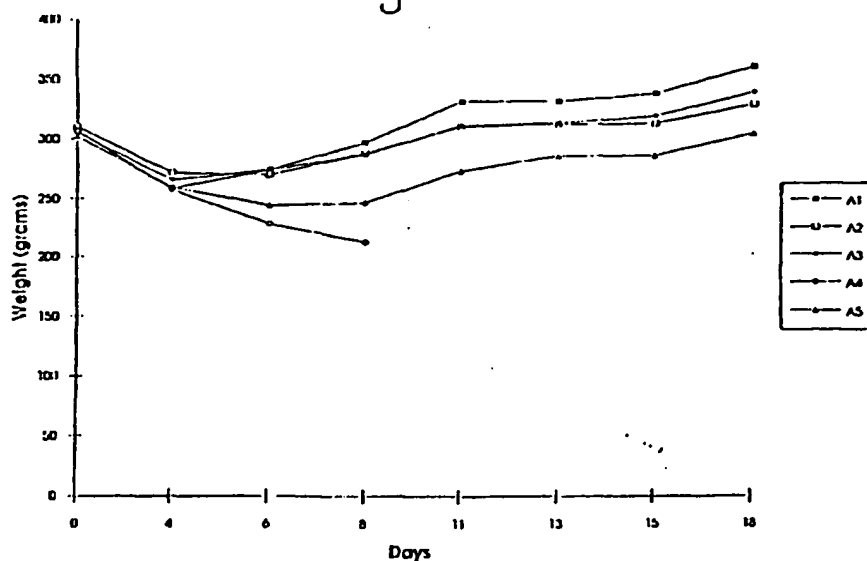
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(54) Composition for the treatment of intestinal wounds or ulcers containing proteins, carbohydrates and fat

(57) The invention relates to the manufacture of a therapeutic composition for aiding healing or preventing the onset of intestinal wounds or ulcers in a patient, reducing, or preventing, the gastrointestinal side effects

associated with the administration of a nonsteroidal anti-inflammatory drug, or treatment of arthritis. The composition includes a protein source, a carbohydrate source, a fat source, and may include a specialised vitamin and mineral profile.

Figure 1



EP 0 699 444 A3



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## EUROPEAN SEARCH REPORT

Application Number  
EP 95 30 6124

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The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 12 March 1999	Examiner ISERT B.
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# EUROPEAN SEARCH REPORT

Application Number  
EP 95 30 6124

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The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 12 March 1999	Examiner ISERT B.
<b>CATEGORY OF CITED DOCUMENTS</b> X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document	

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